Does Ventilator-induced Lung Injury Initiate Non-pulmonary Organ Dysfunction?

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Introduction

The mortality rate and costs associated with acute respiratory distress syndrome (ARDS), the most severe form of acute lung injury (ALI), remain excessively high [1]. Although the most obvious clinical abnormalities in ALI/ARDS are referable to the lung, the most common cause of death is not due to hypoxia but to multiple organ dysfunction syndrome (MODS) [2]. MODS is often irreversible with a mortality rate higher than 60%. We currently lack a specific treatment of the syndrome and modern technology, such as hemodialysis, only allows temporary substitution of organ function, providing a bridge to recovery. Better understanding of the pathophysiology leading to the development of MODS in mechanically ventilated patients should help in the development of approaches to interrupt the cascades leading to MODS.

Most ALI/ARDS patients require mechanical ventilation. Employing low tidal volumes (VT), limited airway pressures, and positive end expiratory pressure (PEEP) during ventilation of injured lungs has not only been shown to attenuate ventilator-induced lung injury (VILI) [3], but has also been shown to decrease non-pulmonary organ dysfunction [4, 5], and mortality in patients with ALI/ARDS [4]. Despite intense research, the mechanisms by which mechanical ventilation ultimately culminates in MODS and death in these patients and how a protective ventilatory strategy would reduce mortality and MODS are only incompletely understood. The coexistence of ARDS and dysfunction of non-pulmonary organs in critically ill patients makes it difficult to determine whether there is a direct causal relationship between mechanical ventilation and the development of MODS. Nevertheless, in view of experimental and human data, it is reasonable to assume that in many instances, injurious mechanical ventilation potentiates the adverse effects of an underlying critical illness and worsens non-pulmonary organ dysfunction.

With this chapter, we wish to review and integrate some of the most pertinent concepts likely to be crucial in the translation of VILI to non-pulmonary organ dysfunction. We structure the chapter into

- mechanical ventilation-induced and propagated lung and systemic inflammatory response,
- mechanical ventilation-induced pro-apoptotic pathways,
- mechanical ventilation-induced impairment of global hemodynamics and oxygen delivery (DO₂),
- mechanical ventilation in ALI/ARDS and kidney dysfunction,
- mechanical ventilation in ALI/ARDS and dysfunction of organs in the hepatosplanchnic region.
Mechanical Ventilation-induced and Propagated Lung and Systemic Inflammatory Response

Two primary mechanistic factors, summarized as mechanotrauma, contribute to the evolution of VILI:
1) exposure of lung tissue to high airway pressures (Paw) resulting in high trans-pulmonary pressures and overdistention of alveolar regions, and
2) cyclic and repetitive alveolar recruitment and derecruitment (collapse) resulting in alveolar shear-stress forces [6].

Alveolar overdistension and shear-forces can stimulate lung and immune cells to produce and release inflammatory cytokines and chemokines – a process termed biotrauma [3]. Concomitant disruption of tissue and cell integrity as well as disruption of lung epithelial and endothelial barriers enables spill-over of inflammatory mediators into the bloodstream resulting in initiation, exacerbation, or propagation of a systemic inflammatory response [7]. The concept that VILI initiates and propagates a systemic inflammatory response that may eventually contribute to the onset of MODS was already suggested almost a decade ago [8]. Mechanical ventilation of injured lungs as compared to healthy lungs consistently results in release of larger amounts of inflammatory mediators into bronchoalveolar lavage (BAL) fluid and blood, and low VT as compared to high VT normally attenuates the release of cytokines and chemokines by the lungs [6]. Given that the vast aerated surface area of the lung is perfused by almost the entire cardiac output, it is conceivable that release of even small quantities of inflammatory mediators per cell could accumulate to a significant amount of these mediators in the circulating blood.

Furthermore, mechanical ventilation-induced disruption of epithelial and endothelial barriers has also been shown to facilitate translocation of intratracheally instilled bacteria and endotoxin from the lung into the blood [9]. Lin et al. instilled Pseudomonas aeruginosa intratracheally in rats and ventilated the animals for one hour followed by extubation. The rats ventilated with an injurious strategy tended to have higher 48-h mortality and were more likely to have a positive blood bacterial culture and an impaired host defense reflected by lower blood and lung levels cytokines as compared to animals subjected to lung protective mechanical ventilation before bacteria instillation [10]. Development of bloodstream infections acquired during an intensive care unit (ICU) stay is associated with mechanical ventilation and was identified as an independent risk factor for death from critical illness [11].

Clinical trials support the concept that biotrauma ultimately leads to MODS. Mechanical ventilation of patients with ALI/ARDS with low VT (about 6 ml/kg predicted body weight) as compared to higher VT (about 12 ml/kg predicted body weight) decreased serum cytokine levels [4, 12], decreased levels of organ dysfunction [4], and decreased mortality [4]. Furthermore, changes in serum levels of pro-inflammatory mediators were found to be associated with changes in overall MODS score [5].

Despite an increasing body of evidence supporting the concept that systemic up-regulation of an inflammatory response associated with mechanical ventilation ultimately contributes to the pathogenesis of MODS, the specific mechanisms remain undefined.

Activated neutrophils appear to play a central role in generation of the tissue injury characteristic of VILI. The lung contains a large pool of margination neutro-